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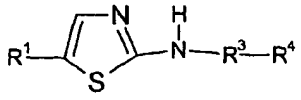
(54) Thiazole derivatives and their use as cdk inhibitors

(57) The invention provides compounds of formula 1



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wherein R^1, R^3, and R^4 are as defined, and their pharmaceutically acceptable salts. Compounds of formula 1 are indicated to have activity inhibiting cdk5, cdk2, and GSK-3. Pharmaceutical compositions and methods comprising compounds of formula 1 for treating diseases and conditions comprising abnormal cell growth, such as cancer, and neurodegenerative diseases and conditions and those affected by dopamine neurotransmission are described. Also described are pharmaceutical compositions and methods comprising compounds of formula 1 for treating male fertility and sperm motility; diabetes mellitus; impaired glucose tolerance; metabolic syndrome or syndrome X; polycystic ovary syndrome; adipogenesis and obesity; myogenesis and frailty, for example age-related decline in physical performance; acute sarcopenia, for example muscle atrophy and/or cachexia associated with burns, bed rest, limb immobilization, or major thoracic, abdominal, and/or orthopedic surgery; sepsis; hair loss, hair thinning, and balding; and immunodeficiency.

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Description

Field of the Invention

[0001] The subject invention relates to thiazole derivatives, pharmaceutical compositions comprising such derivatives and methods of using such derivatives to treat abnormal cell growth and certain diseases and conditions of the central nervous system. The compounds of the present invention act as inhibitors of cyclin-dependent protein kinase enzymes cdk5 (cyclin-dependent protein kinase 5) and cdk2 (cyclin-dependent protein kinase 2). The compounds of the present invention also are inhibitors of the enzyme GSK-3 (glygogen synthase kinase-3) enzyme.

Background of the Invention

[0002] The serine/threonine kinase cdk5 along with its cofactor p25 (or the longer cofactor, p35) has been linked to neurodegenerative disorders, and inhibitors of cdk5/p25 (or cdk5/p35) are therefore useful for the treatment of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, stroke, or Huntington's disease. Treatment of such neurodegenerative disorders using cdk5 inhibitors is supported by the finding that cdk5 is involved in the phosphorylation of tau protein *(J. Biochem,* 117, 741-749 (1995)). cdk5 also phosphorylates Dopamine and Cyclic AMP-Regulated Phosphorprotein (DARPP-32) at threonine 75 and is thus indicated in having a role in dopaminergic neurotransmission *(Nature,* 402, 669-671 (1999)).

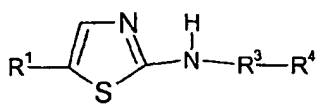
[0003] The serine/threonine kinase cdk2 is essential for normal cell cycling and plays a critical role in disorders arising from abnormal cell cycling, a common characteristic of many oncological disorders. Inhibitors of cdk2 are therefore useful for the treatment of various types of cancer and other diseases or conditions related to abnormal cell growth (Meijer, et al., Properties and Potential-applications of Chemical Inhibitors of Cyclin-dependent Kinsases, *Pharmacology & therapeutics,* 82 (2-3), 279-284 (1999); Sausville, et al., Cyclin-dependent Kinases: Initial Approaches to Exploit a Novel Therapeutic Target, *Pharmacology & therapeutics* 82 (2-3) 285-292 (1999)).

[0004] GSK-3 is a serine/threonine protein kinase. It is one of several protein kinases which phosphorylate glycogen synthase (Embi, et al., *Eur. J. Biochem.* 107:519-527 (1980); Hemmings, et al., *Eur. J. Biochem.* 119:443-451 (1982)). GSK-3 exists in two isoforms, α and β, in vertebrates, reported as having a monomeric structure of 49kD and 47kD respectively. Both isoforms phosphorylate muscle glycogen synthase (Cross, et al., *Biochemical Journal* 303: 21-26 (1994)). The amino acid identity among GSK-3 species homologs has been indicated to be in excess of 98% within the catalytic domain (Plyte, et al., *Biochim. Biophys. Acta* 1114:147-162) (1992)). Due to a remarkably high degree of conservation across the phylogenetic spectrum, a fundamental role of GSK-3 in cellular processes is suggested.

[0005] GSK-3 has been implicated in numerous different disease states and conditions. For example, Chen, et al, *Diabetes* 43: 1234-1241 (1994) have suggested that an increase in GSK-3 activity can be important in Type 2 diabetes. Increased GSK-3 expression in diabetic muscle is also though to contribute to the impaired glycogen synthase activity and skeletal muscle insulin resistance present in Type 2 diabetes (Nikoulina, et al., *Diabetes* 49: 263-271 (2000)). Also, a higher activity of a type 1 protein phosphatase measured in immotile sperm was attributed to higher GSK-3 activity and was indicated as responsible for holding the sperm motility in check (Vijayaraghavan, et al. *Biology of Reproduction* 54: 709-718 (1996)). Vijayaraghavan et al. indicate that such results suggest a biochemical basis for the development and regulation of sperm motility and a possible physiological role for a protein phosphatase 1/inhibitor 2/GSK-3 system. GSK-3 activity has also been associated with Alzheimer's disease and mood disorders such as bipolar disorder (WO 97/41854). Among other conditions, GSK-3 has furthermore been implicated in hair loss, schizophrenia, and neurodegeneration, including both chronic neurodegenerative diseases (such as Alzheimer's, *supra)* and neurotrauma, for example stroke, traumatic brain injury, and spinal cord trauma.

Summary of the Invention

[0006] This invention provides compounds of the formula



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wherein R^1 is a straight chain or branched $(C_1\text{-}C_8)$alkyl, a straight chain or branched $(C_2\text{-}C_8)$alkenyl, a straight

chain or branched (C_2-C_8)alkynyl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11}) bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14}) aryl, (5-14 membered) heteroaryl, or ABN-; and wherein R^1 is optionally substituted with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, and R^7;

[0007] A and B are each independently selected from straight or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8)alkynyl, (C_3-C_6)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, and (5-11 membered) heterocycloalkyl; or A and B may be connected to form a 3-8 membered heterocyclic ring optionally containing one or two double bonds and optionally containing one or two further hetero atoms selected independently from O, S, and N; and A and B, or the heterocyclic ring formed thereby, can be optionally independently substituted with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$,$-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$,$-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$,$-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, and R^7;

R^3 is $-C(=O)NR^9$-, $-C(=O)O$-, $-C(=O)(CR^{10}R^{11})_n$-, or $-(CR^{10}R^{11})_n$-;

R^4 is a straight chain or a branched (C_1-C_8)alkyl, a straight chain or a branched (C_2-C_8)alkenyl, a straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, or (5-14 membered) heteroaryl; and wherein R^4 is optionally substituted with from one to three substitutents R^6 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, or R^7;

each R^7, R^8, and R^9 is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14}) aryl, and (5-14 membered) heteroaryl, wherein R^7, R^8, and R^9 are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{10}R^{11}$, $-NR^{10}C(=O)R^{11}$, $-NR^{10}C(=O)OR^{11}$, $-NR^{10}C(=O)NR^{11}R^{12}$, $-NR^{10}S(=O)_2R^{11}$, $-NR^{10}S(=O)_2NR^{11}R^{12}$, $-OR^{10}$, $OC(=O)R^{10}$, $-OC(=O)OR^{10}$, $-OC(=O)NR^{10}R^{11}$, $-OC(=O)SR^{10}$, $-SR^{10}$, $-S(=O)R^{10}$,$-S(=O)_2R^{10}$, $-S(=O)_2NR^{10}R^{11}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, and R^{10};

or, when R^7 and R^8 are as in NR^7R^8, they may instead optionally be connected to form with the nitrogen of NR^7R^8 to which they are attached a heterocycloalkyl moiety of from three to seven ring members, said heterocycloalkyl moiety optionally comprising one or two further heteroatoms independently selected from N, O, and S;

each R^{10}, R^{11}, and R^{12} is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{10}, R^{11}, and R^{12} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{13}R^{14}$, $-NR^{13}C(=O)R^{14}$, $-NR^{13}C(=O)OR^{14}$, $-NR^{13}C(=O)NR^{14}R^{16}$, $-NR^{13}S(=O)_2R^{14}$, $-NR^{13}S(=O)_2NR^{14}R^{15}$, $-OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13}$, $-OC(=O)NR^{13}R^{14}$, $-OC(=O)SR^{13}$, $-SR^{13}$, $-S(=O)R^{13}$, $-S(=O)_2R^{13}$, $-S(=O)_2NR^{13}R^{14}$, $-C(=O)R^{13}$, $-C(=O)OR^{13}$, $-C(=O)NR^{13}R^{14}$, and R^{13};

each R^{13}, R^{14}, and R^{15} is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl, wherein R^{13}, R^{14}, and R^{15} are each independently optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{16}R^{17}$, $-NR^{16}C(=O)R^{17}$, $-NR^{16}C(=O)OR^{17}$, $-NR^{16}C(=O)NR^{17}R^{18}$, $-NR^{16}S(=O)_2R^{17}$, $-NR^{16}S(=O)_2NR^{17}R^{18}$, $-OR^{16}$, $-OC(=O)R^{16}$, $-OC(=O)OR^{16}$, $-OC(=O)NR^{16}R^{17}$, $-OC(=O)SR^{16}$, $-SR^{16}$, $-S(=O)R^{16}$, $-S(=O)_2R^{16}$, $-S(=O)_2NR^{16}R^{17}$, $-C(=O)R^{16}$, $-C(=O)OR^{16}$, $-C(=O)NR^{16}R^{17}$, and R^{16};

each R^{16}, R^{17}, and R^{18} is independently selected from H, straight chain or branched (C_1-C_8)alkyl, straight chain or branched (C_2-C_8)alkenyl, straight chain or branched (C_2-C_8 alkynyl), (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl, (3-8 membered) heterocycloalkyl, (C_5-C_{11})bicycloalkyl, (C_7-C_{11})bicycloalkenyl, (5-11 membered) heterobicycloalkyl, (C_6-C_{14})aryl, and (5-14 membered) heteroaryl;

n is 0, 1, 2, or 3;

wherein R^{10} and R^{11} in $-C(=O)(CR^{10}R^{11})_n$- and $-(CR^{10}R^{11})_n$- are for each iteration of n defined independently as recited above;

and pharmaceutically acceptable salts thereof.

[0008] Compounds of formula **1** of the invention are inhibitors of serine/threonine kinases, especially cyclin-dependent kinases such as cdk5 and cdk2, and are useful for the treatment of neurodegenerative disorders and other CNS disorders, and of abnormal cell growth, including cancer. The compounds of formula **1** are particularly useful in inhibiting cdk5. Compounds of formula **1** are furthermore also useful as inhibitors of GSK-3.

[0009] The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, and *t*-butyl.

[0010] The term "alkenyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples of alkenyl include, but are not limited to, ethenyl and propenyl.

[0011] The term "alkynyl", as used herein, unless otherwise indicated, includes alkyl moieties having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl.

[0012] The term "cycloalkyl", as used herein, unless otherwise indicated, includes non-aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. "Bicycloalkyl" groups are non-aromatic saturated carbocyclic groups consisting of two rings, wherein said rings share one or two carbon atoms. For purposes of the present invention, and unless otherwise indicated, bicycloalkyl groups include spiro groups and fused ring groups. Examples of bicycloalkyl groups include, but are not limited to, bicyclo-[3.1.0]-hexyl, norbornyl, spiro[4.5]decyl, spiro[4.4]nonyl, spiro[4.3]octyl, and spiro [4.2]heptyl. "Cycloalkenyl" and "bicycloalkenyl" refer to non-aromatic carbocyclic cycloalkyl and bicycloalkyl moieties as defined above, except comprising one or more carbon-carbon double bonds connecting carbon ring members (an "endocyclic" double bond) and/or one or more carbon-carbon double bonds connecting a carbon ring member and an adjacent non-ring carbon (an "exocyclic" double bond). Examples of cycloalkenyl groups include, but are not limited to, cyclopentenyl and cyclobutenyl, and a non-limiting example of a bicycloalkenyl group is norbornenyl. Cycloalkyl, cycloalkenyl, bicycloalkyl, and bicycloalkenyl groups also include groups that are substituted with one or more oxo moieties. Examples of such groups with oxo moieties are oxocyclopentyl, oxocyclobutyl, oxocyclopentenyl, and norcamphoryl.

[0013] The term "aryl", as used herein, unless otherwise indicated, includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl, naphthyl, indenyl, and fluorenyl.

[0014] The terms "heterocyclic", "heterocycloalkyl", and like terms, as used herein, refer to non-aromatic cyclic groups containing one or more heteroatoms, prefereably from one to four heteroatoms, each selected from O, S and N. "Heterobicycloalkyl" groups are non-aromatic two-ringed cyclic groups, wherein said rings share one or two atoms, and wherein at least one of the rings contains a heteroatom (O, S, or N). Heterobicycloalkyl groups for purposes of the present invention, and unless otherwise indicated, include spiro groups and fused ring groups. In one embodiment, each ring in the heterobicycloalkyl contains up to four heteroatoms (i.e. from zero to four heteroatoms, provided that at least one ring contains at least one heteroatom). The heterocyclic groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of non-aromatic heterocyclic groups are aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-tetrahydropyridinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholino, thiomorpholino, thioxanyl, pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, quinolizinyl, quinuclidinyl, 1,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, 1,4-dioxaspiro[4.3]octyl, and 1,4-dioxaspiro[4.2]heptyl.

[0015] "Heteroaryl", as used herein, refers to aromatic groups containing one or more heteroatoms (O, S, or N), preferably from one to four heteroatoms. A multicyclic group containing one or more heteroatoms wherein at least one ring of the group is aromatic is a "heteroaryl" group. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. Examples of heteroaryl groups are pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.

[0016] The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). The terms referring to the groups also encompass all possible tautomers.

[0017] In one embodiment, this invention provides compounds of formula **1**, wherein R^1 is cyclobutyl, optionally substituted with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$,$-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$,$-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, -S

$(=O)_2NR^7R^8$, and R^7. In a further embodiment, R^1 is cyclobutyl and R^3 is $-C(=O)(CR^{10}R^{11})_n-$.

[0018] In another embodiment of the invention, compounds of formula **1** are provided wherein R^1 is ABN-.

[0019] In another embodiment of the invention, compounds of formula **1** are provided wherein R^3 is $-(CR^{10}R^{11})_0-$ (in other words, R^3 is a bond), and R^4 is (3-8 membered) heterocycloalkyl, (C_6-C_{14})aryl, or (5-14 membered) heteroaryl, and R^4 is optionally substituted with from one to three substitutents R^6 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$,$-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$,$-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, or R^7. In a further embodiment of compounds of formula **1** wherein R^3 is a bond, R^4 is (C_6-C_{14}) aryl or (5-14 membered) heteroaryl, each optionally substituted. In a more preferred embodiment wherein R^3 is a bond, R^4 is optionally substituted phenyl or optionally substituted pyridyl. In another preferred embodiment wherein R^3 is a bond, R^4 is naphthyl, quinolyl, or isoquinolyl, each optionally substituted. In another embodiment wherein R^3 is a bond, R^4 is napthyl, quinolyl, or isoquinolyl, and is unsubstituted.

[0020] In another embodiment of the invention, R^3 is a bond and R^1 is optionally substituted straight chain or branched (C_1-C_8)alkyl or optionally substituted straight chain or branched (C_2-C_8)alkenyl

[0021] In another embodiment, this invention provides compounds of formula **1**, wherein R^3 is-$C(=O)NR^9$- or $-C(=O)(CR^{10}R^{11})_n-$. In another embodiment, R^{10} and R^{11} of $-C(=O)(CR^{10}R^{11})_n-$ are at each iteration of n both hydrogen. In another embodiment, R^9 of $-C(=O)NR^9-$ is hydrogen. In another embodiment, and R^3 is $-C(=O)NR^9-$ or $-C(=O)(CR^{10}R^{11})_n-$.

[0022] In another embodiment of the invention, a compound of formula **1** is provided wherein R^1 is optionally substituted (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl. Preferred embodiments are wherein R^1 is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, each optionally substituted as recited above (i.e. optionally with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C(=O)NR^8R^9$, $-NR^7S(=O)_2R^8$, $-NR^7S(=O)_2NR^8R^9$, $-OR^7$, $-OC(=O)R^7$, $-OC(=O)OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, $-C(=O)NR^7R^8$, $-OC(=O)NR^7R^8$, $-OC(=O)SR^7$, $-SR^7$, $-S(=O)R^7$, $-S(=O)_2R^7$, $-S(=O)_2NR^7R^8$, and R^7). In a more preferred embodiment, R^1 is (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, and is optionally substituted with from one to three substituents independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-OR^7$, $-C(=O)OR^7$, $-C(=O)R^7$, and R^7. More preferably, R^1 is (C_3-C_8)cycloalkyl or optionally substituted (C_5-C_{11}) bicycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or norbornyl, and R^1 is substituted with $-NR^7C(=O)R^8$, (C_6-C_{14})aryl, (3-8 membered) heterocycloalkyl, or (5-14 membered) heteroaryl, and wherein said aryl, heterocycloalkyl, and heteroaryl are each optionally substituted with from one to six substituents independently selected from F, Cl, Br, I, NO_2, -CN, $-CF_3$, $-NR^{10}R^{11}$, $-NR^{10}C(=O)R^{11}$, $-NR^{10}C(=O)OR^{11}$, $-NR^{10}C(=O)NR^{11}R^{12}$, $-NR^{10}S(=O)_2R^{11}$, $-NR^{10}S(=O)_2NR^{11}R^{12}$, $-OR^{10}$, $-OC(=O)R^{10}$, $-OC(=O)OR^{10}$, $-OC(=O)NR^{10}R^{11}$, $-OC(=O)SR^{10}$, $-SR^{10}$, $-S(=O)R^{10}$, $-S(=O)_2R^{10}$, $-S(=O)_2NR^{10}R^{11}$, $-C(=O)R^{10}$, $-C(=O)OR^{10}$, $-C(=O)NR^{10}R^{11}$, and R^{10}. In another embodiment of the invention, R^1 is bicyclo-[3.1.0]-hexyl and is optionally substituted as recited above (i.e. optionally substituted with from one to six substituents R^5 independently selected from F, Cl, Br, I, nitro, cyano, $-CF_3$, $-NR^7R^8$, $-NR^7C(=O)R^8$, $-NR^7C(=O)OR^8$, $-NR^7C$

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